# General

## Guideline Title

Care of dying adults in the last days of life.

## Bibliographic Source(s)

National Clinical Guideline Centre. Care of dying adults in the last days of life. London (UK): National Institute for Health and Care Excellence (NICE); 2015 Dec 16. 26 p. (NICE guideline; no. 31).

## Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

# Regulatory Alert

## FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- August 31, 2016 – Opioid pain and cough medicines combined with benzodiazepines : A U.S. Food and Drug Administration (FDA) review has found that the growing combined used of opioid medicines with benzodiazepines or other drugs that depress the central nervous system (CNS) has resulted in serious side effects, including slowed or difficult breathing and deaths. FDA is adding Boxed Warnings to the drug labeling of prescription opioid pain and prescription opioid cough medicines and benzodiazepines.
- May 10, 2016 – Olanzapine : The U.S. Food and Drug Administration (FDA) is warning that the antipsychotic medicine olanzapine can cause a rare but serious skin reaction that can progress to affect other parts of the body. FDA is adding a new warning to the drug labels for all olanzapine-containing products that describes this severe condition known as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).
- March 22, 2016 – Opioid pain medicines : The U.S. Food and Drug Administration (FDA) is warning about several safety issues with the entire class of opioid pain medicines. These safety risks are potentially harmful interactions with numerous other medications, problems with the adrenal glands, and decreased sex hormone levels. They are requiring changes to the labels of all opioid drugs to warn about these risks.

# Recommendations

# Major Recommendations

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Clinical Guideline Centre (NCGC) on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance and related appendices.

The wording used in the recommendations in this guideline (for example, words such as 'offer' and 'consider') denotes the certainty with which the recommendation is made (the strength of the recommendation) and is defined at the end of the "Major Recommendations" field.

Recognising When a Person May Be in the Last Days of Life

These recommendations are intended to help healthcare professionals to recognise when a person may be entering the last days of their life, or if they may be deteriorating, stabilising or improving even temporarily. It can often be difficult to be certain that a person is dying. The recommendations supplement the individual clinical judgement that is needed to make decisions about the level of certainty of prognosis and how to manage any uncertainty.

If it is thought that a person may be entering the last days of life, gather and document information on:

- The person's physiological, psychological, social and spiritual needs
- Current clinical signs and symptoms
- Medical history and the clinical context, including underlying diagnoses
- The person's goals and wishes
- The views of those important to the person about future care

Assess for changes in signs and symptoms in the person and review any investigation results that have already been reported that may suggest a person is entering the last days of life. These changes include the following:

- Signs such as agitation, Cheyne–Stokes breathing, deterioration in level of consciousness, mottled skin, noisy respiratory secretions and progressive weight loss
- Symptoms such as increasing fatigue and loss of appetite
- Functional observations such as changes in communication, deteriorating mobility or performance status, or social withdrawal

Be aware that improvement in signs and symptoms or functional observations could indicate that the person may be stabilising or recovering.

Avoid undertaking investigations that are unlikely to affect care in the last few days of life unless there is a clinical need to do so, for example, when a blood count could guide the use of platelet transfusion to avoid catastrophic bleeding.

Use the knowledge gained from the assessments and other information gathered from the multiprofessional team, the person and those important to them, to help determine whether the person is nearing death, deteriorating, stable or improving.

Monitor for further changes in the person at least every 24 hours and update the person's care plan.

Seek advice from colleagues with more experience of providing end of life care when there is a high level of uncertainty (for example, ambiguous or conflicting clinical signs or symptoms) about whether a person is entering the last days of life, may be stabilising or if there is potential for even temporary recovery.

Communication

Please also refer to the recommendations on communication in NICE's guideline on Patient experience in adult NHS services .

Healthcare professionals caring for adults at the end of life need to take into consideration the person's current mental capacity to communicate and actively participate in their end of life care (for more information see Your care ).

Establish the communication needs and expectations of people who may be entering their last days of life, taking into account:

- If they would like a person important to them to be present when making decisions about their care
- Their current level of understanding that they may be nearing death
- Their cognitive status and if they have any specific speech, language or other communication need
- How much information they would like to have about their prognosis

- Any cultural, religious, social or spiritual needs or preferences

Identify the most appropriate available multiprofessional team member to explain the dying person's prognosis. Base this decision on the professional's:

- Competence and confidence
- Rapport with the person

Discuss the dying person's prognosis with them (unless they do not wish to be informed) as soon as it is recognised that they may be entering the last days of life and include those important to them in the discussion if the dying person wishes.

Provide the dying person, and those important to them, with:

- Accurate information about their prognosis (unless they do not wish to be informed), explaining any uncertainty and how this will be managed, but avoiding false optimism
- An opportunity to talk about any fears and anxieties, and to ask questions about their care in the last days of life
- Information about how to contact members of their care team
- Opportunities for further discussion with a member of their care team

Explore with the dying person and those important to them:

- Whether the dying person has an advance statement or has stated preferences about their care in the last days of life (including any anticipatory prescribing decisions or an advance decision to refuse treatment or details of any legal lasting power of attorney for health and welfare)
- Whether the dying person has understood and can retain the information given about their prognosis

Discuss the dying person's prognosis with other members of the multiprofessional care team, and ensure that this is documented in the dying person's record of care.

Shared Decision-Making

The recommendations in this section cover shared decision-making in the last days of life. Healthcare professionals caring for adults at the end of life need to take into consideration the person's current mental capacity to engage and actively participate in shared decision-making on their end of life care (for more information see Your care ).

Please also refer to the recommendations on shared decision-making in NICE's guideline on Patient experience in adult NHS services .

Establish the level of involvement that the dying person wishes to have and is able to have in shared decision-making, and ensure that honesty and transparency are used when discussing the development and implementation of their care plan.

As part of any shared decision-making process take into account:

- Whether the dying person has an advance statement or an advance decision to refuse treatment in place, or has provided details of any legal lasting power of attorney for health and welfare
- The person's current goals and wishes
- Whether the dying person has any cultural, religious, social or spiritual preferences

Identify a named lead healthcare professional, who is responsible for encouraging shared decision-making in the person's last days of life. The named healthcare professional should:

- Give information about how they can be contacted and contact details for relevant out-of-hours services to the dying person and those important to them
- Ensure that any agreed changes to the care plan are understood by the dying person, those important to them, and those involved in the dying person's care

Providing Individualised Care

Establish as early as possible the resources needed for the dying person (for example, the delivery of meals, equipment, care at night, volunteer support or assistance from an organisation) and their availability.

In discussion with the dying person, those important to them and the multiprofessional team, create an individualised care plan. The plan should include the dying person's:

- Personal goals and wishes
- Preferred care setting
- Current and anticipated care needs including:
    - Preferences for symptom management
    - Needs for care after death, if any are specified
- Resource needs

Record individualised care plan discussions and decisions in the dying person's record of care and share the care plan with the dying person, those important to them and all members of the multiprofessional care team.

Continue to explore the understanding and wishes of the dying person and those important to them, and update the care plan as needed. Recognise that the dying person's ability and desire to be involved in making decisions about their care may change as their condition deteriorates or as they accept their prognosis.

While it is normally possible and desirable to meet the wishes of a dying person, when this is not possible explain the reason why to the dying person and those important to them.

Ensure that shared decision-making can be supported by experienced staff at all times. Seek further specialist advice if additional support is needed.

Maintaining Hydration

Support the dying person to drink if they wish to and are able to. Check for any difficulties, such as swallowing problems or risk of aspiration. Discuss the risks and benefits of continuing to drink, with the dying person, and those involved in the dying person's care.

Offer frequent care of the mouth and lips to the dying person, and include the management of dry mouth in their care plan, if needed. Offer the person the following, as needed:

- Help with cleaning their teeth or dentures, if they would like
- Frequent sips of fluid

Encourage people important to the dying person to help with mouth and lip care or giving drinks, if they wish to. Provide any necessary aids and give them advice on giving drinks safely.

Assess, preferably daily, the dying person's hydration status, and review the possible need for starting clinically assisted hydration, respecting the person's wishes and preferences.

Discuss the risks and benefits of clinically assisted hydration with the dying person and those important to them. Advise them that, for someone who is in the last days of life:

- Clinically assisted hydration may relieve distressing symptoms or signs related to dehydration, but may cause other problems (see recommendation below)
- It is uncertain if giving clinically assisted hydration will prolong life or extend the dying process
- It is uncertain if not giving clinically assisted hydration will hasten death

Ensure that any concerns raised by the dying person or those important to them are addressed before starting clinically assisted hydration.

When considering clinically assisted hydration for a dying person, use an individualised approach and take into account:

- Whether they have expressed a preference for or against clinically assisted hydration, or have any cultural, spiritual or religious beliefs that might affect this documented in an advance statement or an advance decision to refuse treatment
- Their level of consciousness
- Any swallowing difficulties
- Their level of thirst
- The risk of pulmonary oedema
- Whether even temporary recovery is possible

Consider a therapeutic trial of clinically assisted hydration if the person has distressing symptoms or signs that could be associated with dehydration, such as thirst or delirium, and oral hydration is inadequate.

For people being started on clinically assisted hydration:

- Monitor at least every 12 hours for changes in the symptoms or signs of dehydration, and for any evidence of benefit or harm.
- Continue with clinically assisted hydration if there are signs of clinical benefit.
- Reduce or stop clinically assisted hydration if there are signs of possible harm to the dying person, such as fluid overload, or if they no longer want it.

For people already dependent on clinically assisted hydration (enteral or parenteral) before the last days of life:

- Review the risks and benefits of continuing clinically assisted hydration with the person and those important to them.
- Consider whether to continue, reduce or stop clinically assisted hydration as the person nears death.

Pharmacological Interventions

Providing appropriate non-pharmacological methods of symptom management is an important part of high-quality care at the end of life, for example, re-positioning to manage pain or using fans to minimise the impact of breathlessness, but this has not been addressed in this guideline. This section focuses on the pharmacological management of common symptoms at the end of life and includes general recommendations for non-specialists prescribing medicines to manage these symptoms.

When it is recognised that a person may be entering the last days of life, review their current medicines and, after discussion and agreement with the dying person and those important to them (as appropriate), stop any previously prescribed medicines that are not providing symptomatic benefit or that may cause harm.

When involving the dying person and those important to them in making decisions about symptom control in the last days of life:

- Use the dying person's individualised care plan to help decide which medicines are clinically appropriate.
- Discuss the benefits and harms of any medicines offered.

When considering medicines for symptom control, take into account:

- The likely cause of the symptom
- The dying person's preferences alongside the benefits and harms of the medicine
- Any individual or cultural views that might affect their choice
- Any other medicines being taken to manage symptoms
- Any risks of the medicine that could affect prescribing decisions, for example, prescribing cyclizine to manage nausea and vomiting may exacerbate heart failure

Decide on the most effective route for administering medicines in the last days of life tailored to the dying person's condition, their ability to swallow safely and their preferences.

Consider prescribing different routes of administering medicine if the dying person is unable to take or tolerate oral medicines. Avoid giving intramuscular injections and give either subcutaneous or intravenous injections.

Consider using a syringe pump to deliver medicines for continuous symptom control if more than 2 or 3 doses of any 'as required' medicines have been given within 24 hours.

For people starting treatment who have not previously been given medicines for symptom management, start with the lowest effective dose and titrate as clinically indicated.

Regularly reassess, at least daily, the dying person's symptoms during treatment to inform appropriate titration of medicine.

Seek specialist palliative care advice if the dying person's symptoms do not improve promptly with treatment or if there are undesirable side effects, such as unwanted sedation.

Managing Pain

Consider non-pharmacological management of pain in a person in the last days of life.

Be aware that not all people in the last days of life experience pain. If pain is identified, manage it promptly and effectively, and treat any reversible causes of pain, such as urinary retention.

Assess the dying person's level of pain and assess for all possible causes when making prescribing decisions for managing pain.

Follow the principles of pain management used at other times when caring for people in the last days of life, for example, matching the medicine to the severity of pain and, when possible, using the dying person's preferences for how it is given.

For a person who is unable to effectively explain that they are in pain, for example someone with dementia or learning disabilities, use a validated behavioural pain assessment to inform their pain management.

Managing Breathlessness

Identify and treat reversible causes of breathlessness in the dying person, for example pulmonary oedema or pleural effusion.

Consider non-pharmacological management of breathlessness in a person in the last days of life. Do not routinely start oxygen to manage breathlessness. Only offer oxygen therapy to people known or clinically suspected to have symptomatic hypoxaemia.

Consider managing breathlessness with:

- An opioid[1] or
- A benzodiazepine[1] or
- A combination of an opioid[1] and benzodiazepine[1]

Managing Nausea and Vomiting

Assess for likely causes of nausea or vomiting in the dying person. These may include:

- Certain medicines that can cause or contribute to nausea and vomiting
- Recent chemotherapy or radiotherapy
- Psychological causes
- Biochemical causes, for example hypercalcaemia
- Raised intracranial pressure
- Gastrointestinal motility disorder
- Ileus or bowel obstruction

Discuss the options for treating nausea and vomiting with the dying person and those important to them.

Consider non-pharmacological methods for treating nausea and vomiting in a person in the last days of life.

When choosing medicines to manage nausea or vomiting in a person in the last days of life, take into account:

- The likely cause and if it is reversible
- The side effects, including sedative effects, of the medicine
- Other symptoms the person has
- The desired balancing of effects when managing other symptoms
- Compatibility and drug interactions with other medicines the person is taking

For people in the last days of life with obstructive bowel disorders who have nausea or vomiting, consider:

- Hyoscine butylbromide[1] as the first-line pharmacological treatment
- Octreotide[1] if the symptoms do not improve within 24 hours of starting treatment with hyoscine butylbromide[1]

Managing Anxiety, Delirium and Agitation

Explore the possible causes of anxiety or delirium, with or without agitation, with the dying person and those important to them. Be aware that agitation in isolation is sometimes associated with other unrelieved symptoms or bodily needs, for example, unrelieved pain or a full bladder or rectum.

Consider non-pharmacological management of agitation, anxiety and delirium in a person in the last days of life.

Treat any reversible causes of agitation, anxiety or delirium, for example, psychological causes or certain metabolic disorders (for example, renal failure or hyponatraemia).

Consider a trial of a benzodiazepine to manage anxiety or agitation.

Consider a trial of an antipsychotic medicine to manage delirium or agitation.

Seek specialist advice if the diagnosis of agitation or delirium is uncertain, if the agitation or delirium does not respond to antipsychotic treatment or if treatment causes unwanted sedation.

Managing Noisy Respiratory Secretions

Assess for the likely causes of noisy respiratory secretions in people in the last days of life. Establish whether the noise has an impact on the dying person or those important to them. Reassure them that, although the noise can be distressing, it is unlikely to cause discomfort. Be prepared to talk about any fears or concerns they may have.

Consider non-pharmacological measures to manage noisy respiratory or pharyngeal secretions, to reduce any distress in people at the end of life.

Consider a trial of medicine to treat noisy respiratory secretions if they are causing distress to the dying person. Tailor treatment to the dying person's individual needs or circumstances, using 1 of the following drugs:

- Atropine[1] or
- Glycopyrronium bromide[1] or
- Hyoscine butylbromide[1] or
- Hyoscine hydrobromide[1]

When giving medicine for noisy respiratory secretions:

- Monitor for improvements, preferably every 4 hours, but at least every 12 hours.
- Monitor regularly for side effects, particularly delirium, agitation or excessive sedation when using atropine or hyoscine hydrobromide.
- Treat side effects, such as dry mouth, delirium or sedation (see relevant recommendations above).

Consider changing or stopping medicines if noisy respiratory secretions continue and are still causing distress after 12 hours (medicines may take up to 12 hours to become effective).

Consider changing or stopping medicines if unacceptable side effects, such as dry mouth, urinary retention, delirium, agitation and unwanted levels of sedation, persist.

Anticipatory Prescribing

Use an individualised approach to prescribing anticipatory medicines for people who are likely to need symptom control in the last days of life. Specify the indications for use and the dosage of any medicines prescribed.

Assess what medicines the person might need to manage symptoms likely to occur during their last days of life (such as agitation, anxiety, breathlessness, nausea and vomiting, noisy respiratory secretions and pain). Discuss any prescribing needs with the dying person, those important to them and the multiprofessional team.

Ensure that suitable anticipatory medicines and routes are prescribed as early as possible. Review these medicines as the dying person's needs change.

When deciding which anticipatory medicines to offer take into account:

- The likelihood of specific symptoms occurring
- The benefits and harms of prescribing or administering medicines
- The benefits and harms of not prescribing or administering medicines
- The possible risk of the person suddenly deteriorating (for example, catastrophic haemorrhage or seizures) for which urgent symptom control may be needed
- The place of care and the time it would take to obtain medicines

Before anticipatory medicines are administered, review the dying person's individual symptoms and adjust the individualised care plan and

prescriptions as necessary.

If anticipatory medicines are administered:

- Monitor for benefits and any side effects at least daily, and give feedback to the lead healthcare professional.
- Adjust the individualised care plan and prescription as necessary.

Footnote

[1]At the time of publication (December 2015), this medication did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

Definitions

Strength of Recommendations

Some recommendations can be made with more certainty than others. The Guideline Committee makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the Guideline Committee is confident that, given the information it has looked at, most patients would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

*Interventions That Must (or Must Not) Be Used*

The Guideline Committee usually uses 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally the Guideline Committee uses 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

*Interventions That Should (or Should Not) Be Used – a 'Strong' Recommendation*

The Guideline Committee uses 'offer' (and similar words such as 'refer' or 'advise') when confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. The Guideline Committee uses similar forms of words (for example, 'Do not offer…') when confident that an intervention will not be of benefit for most patients.

*Interventions That Could Be Used*

The Guideline Committee uses 'consider' when confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

## Clinical Algorithm(s)

None provided

# Scope

## Disease/Condition(s)

- Any disease or condition for which death is expected within a few days
- Difficult symptoms such as pain, anxiety, breathlessness, terminal agitation, nausea, vomiting, and respiratory secretions during the last days of life

## Guideline Category

Counseling

Evaluation

Management

## Clinical Specialty

Critical Care

Family Practice

Geriatrics

Internal Medicine

Nursing

Oncology

## Intended Users

Advanced Practice Nurses

Allied Health Personnel

Health Care Providers

Hospitals

Nurses

Patients

Physician Assistants

Physicians

Psychologists/Non-physician Behavioral Health Clinicians

Respiratory Care Practitioners

Social Workers

Speech-Language Pathologists

## Guideline Objective(s)

- To provide guidance to health and care professionals to enable them to better recognise when a person is dying, and how to communicate and share decisions respectfully with the dying person and those important to them
- To provide guidance on how best to manage difficult symptoms in order to maintain comfort and dignity without causing unacceptable side-effects

## Target Population

Adults (aged 18 years and over) in whom death is expected within a few days

## Interventions and Practices Considered

1. Recognising when a person may be in the last days of life (signs and symptoms)

2. Recognising barriers and establishing facilitators to good communication between the dying person, those important to them, and the healthcare professional
3. Shared decision making
4. Maintaining hydration (use of clinically assisted hydration)
5. Pharmacological interventions to manage pain, breathlessness, nausea and vomiting, anxiety, agitation, delirium, and noisy respiratory secretions
6. General pharmacological considerations
7. Anticipatory prescribing

## Major Outcomes Considered

- Death
- Length of survival
- Quality of life
- Patient or carer satisfaction
- Identification and/or achievement of patient wishes such as preferred place of death
- Subjective or objective symptom improvement
- Hydration status
- Adverse events
- Sedation
- Cost-effectiveness

# Methodology

## Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

## Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Clinical Guideline Centre (NCGC) on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance and related appendices.

Developing the Review Questions and Outcomes

Review questions were developed in a PICO framework (patient, intervention, comparison and outcome) for intervention reviews; in a framework of population, index tests, reference standard and target condition for reviews of diagnostic test accuracy; and using population, presence or absence of factors under investigation (for example, prognostic factors) and outcomes for prognostic reviews.

This use of a framework guided the literature searching process, critical appraisal and synthesis of evidence, and facilitated the development of recommendations by the Committee. The review questions were drafted by the NCGC technical team and refined and validated by the Committee. The questions were based on the key clinical areas identified in the scope (see Appendix A).

As part of the scope a total of 11 questions were identified. During protocol development with the Committee, recognising dying was divided to include both a quantitative and a qualitative component which were then integrated into a framework.

The Committee also decided that pharmacological symptom management of pain, anxiety, breathlessness, agitation and delirium should be combined into 1 question. The rationale for this was that there was likely to be an overlap in the medications and in symptom outcome reporting.

The Committee decided to include both qualitative and quantitative evidence for the topic of anticipatory prescribing (comparing to prescribing at the bedside). The quantitative focus was added to the review topic to identify evidence of data that could inform the associated costs of anticipatory prescribing which would not be possible from qualitative data.

This led to a total of 10 review questions.

Full literature searches, critical appraisals and evidence reviews were completed for all the specified review questions.

Searching for Evidence

Clinical Literature Search

Systematic literature searches were undertaken to identify all published clinical evidence relevant to the review questions. Searches were undertaken according to the parameters stipulated within the NICE guidelines manual (see the "Availability of Companion Documents" field). Databases were searched using relevant medical subject headings, free-text terms and study-type filters where appropriate. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English. All searches were conducted in MEDLINE, EMBASE, and The Cochrane Library. Additional subject specific databases were used for some questions: such as PsycINFO and CINAHL. Searches were not re-run prior to final submission because this guideline is classified as a short guideline.

Search strategies were quality assured by cross-checking reference lists of highly relevant papers, analysing search strategies in other systematic reviews, and asking Committee members to highlight any additional studies. The questions, the study types applied, the databases searched and the dates or years covered can be found in Appendix G.

The titles and abstracts of records retrieved by the searches were sifted for relevance, with potentially significant publications obtained in full text. These were assessed against the inclusion criteria.

During the scoping stage, a search was conducted for guidelines and reports on the websites listed below from organisations relevant to the topic. Searching for unpublished literature was not undertaken. All references sent by stakeholders were considered.

- Guidelines International Network database (www.g-i-n.net )
- NGC (www.guideline.gov )
- NICE (www.nice.org.uk )
- National Institutes of Health Consensus Development Program (consensus.nih.gov )
- National Health Service (NHS) Evidence Search (www.evidence.nhs.uk )

Health Economic Literature Search

Systematic literature searches were also undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to the dying adult in the NHS Economic Evaluation Database (EED), the Health Technology Assessment database (HTA) and the Health Economic Evaluations Database (HEED) with no date restrictions. Additionally, the search was run on MEDLINE and EMBASE from 2013, using a specific economic filter, to ensure recent publications that had not yet been indexed by the economic databases were identified. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English.

The health economic search strategies are included in Appendix G. Searches were not re-run prior to final submission because this guideline is classified as a short guideline.

Evidence of Effectiveness

The evidence was reviewed following the steps shown schematically in Figure 1 in the full version of the guideline.

- Potentially relevant studies were identified for each review question from the relevant search results by reviewing titles and abstracts. Full papers were then obtained.
- Full papers were reviewed against pre-specified inclusion and exclusion criteria to identify studies that addressed the review question in the appropriate population (review protocols are included in Appendix C).

Inclusion and Exclusion Criteria

The inclusion and exclusion of studies was based on the review protocols, which can be found in Appendix C. Excluded studies by review question (with the reasons for their exclusion) are listed in Appendix L. The Committee was consulted about any uncertainty regarding inclusion or

exclusion. There are particular inclusion and exclusion criteria to be highlighted here for the following areas of the scope:

*Guideline Population*

The guideline population was defined to be adults (over 18) in the last days of life, defined as the last 2 to 3 days of life. There was complete agreement in the Committee that in relation to any review of evidence, this should correspond to a population of adults likely to die within 14 days (which has been classified by the Department of Health's review of the Liverpool Care Pathway as 'last days'). This meant that any study with groups of people who have a prognosis of less than 14 days or where qualitative research was aimed at covering this time period were classed as a direct study population. It was recognised that there would be some uncertainty around prognosis for this timeframe and with evidence anticipated to be sparse, it was decided that groups of people with a prognosis of up to 30 days could be considered as an indirect population. Studies that included groups of people described as dying within a timeframe longer than 1 month were excluded from the outset.

*Recognising Dying*

Delphi consensus studies were included for the topic of 'recognising dying' (chapter 6 of the full version of the guideline). The Committee considered Delphi consensus studies applicable for this topic as they provide useful consensus information to support the extracted themes. Furthermore, the quantitative section of this review aimed to identify pre-specified signs and symptoms that were independently related to recognising that a person is in the last days of life, that is, independent of other characteristics. Therefore the focus of the evidence was on studies using multivariable analysis.

In accordance with the scope of the guideline, the role of laboratory and biological evidence was not directly included in this review. This meant that direct search terms for all possible biological tests or markers added were not added to the database search. However, when tests were considered in combination with signs or symptoms to identify a possible combination of clinical presentations that improves the recognition of the last days of life or signs of recovery, then this was included as a surrogate sign or symptom (such as kidney function test results).

*Communication, Shared Decision Making and Anticipatory Prescribing*

Delphi and other descriptive surveys (such as frequency of people who responding to closed-ended questions) were not included in the other qualitative reviews (communication, shared decision making and anticipatory prescribing). The Committee considered qualitative data such as studies using interviews, focus groups, or surveys with rich qualitative open-ended options the most appropriate study design. The shared decision making review focused on evidence from different perspectives (that is, healthcare professionals, the person who is dying, or those important to them) on the barriers and facilitators to shared decision making. There was a large evidence base on this topic but mainly from a healthcare professional perspective; as such the evidence base was restricted to UK studies only. However, there was only 1 UK study on the family's perspective on shared decision making, hence studies from other countries were also included.

*Intervention Reviews (Clinically Assisted Hydration and Pharmacological Symptom Management)*

Randomised controlled trials (RCTs), non-randomised trials, and observational studies (including diagnostic or prognostic studies) were included in the evidence reviews, according to the review protocols. For the intervention reviews, both randomised and non-randomised comparative studies were included to provide the most informative evidence base possible for the Committee decision making.

*Other General Study Type Inclusions or Exclusions*

Conference abstracts were not automatically excluded from the review but were initially assessed against the inclusion criteria and then further processed only if no other full publication was available for that review question, in which case the authors of the selected abstracts were contacted for further information. None of the reviews included evidence from conference abstracts.

Literature reviews, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded. The review protocols are presented in Appendix C.

Evidence of Cost-effectiveness

The Committee is required to make decisions based on the best available evidence of both clinical and cost effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits (that is, their 'cost-effectiveness') rather than the total implementation cost. Thus, if the evidence suggests that a strategy provides significant health benefits at an acceptable cost per person treated, it should be recommended even if it would be expensive to implement across the whole population.

Evidence on cost effectiveness related to the key clinical issues being addressed in the guideline was sought. The health economist undertook a systematic review of the published economic literature.

The health economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts. Full papers were then obtained.
- Reviewed full papers against pre-specified inclusion and exclusion criteria to identify relevant studies.

Inclusion and Exclusion Criteria

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action (cost–utility, cost-effectiveness, cost–benefit and cost–consequences analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially includable as economic evidence.

Studies that only reported cost per hospital (not per person), or only reported average cost effectiveness without disaggregated costs and effects, were excluded. Literature reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded. Studies published before 1999 and studies from non-Organisation for Economic Co-operation and Development (OECD) countries or the USA were also excluded, on the basis that the applicability of such studies to the present UK NHS context is likely to be too low for them to be helpful for decision-making.

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available, then other less relevant studies may not have been included. Where exclusions occurred on this basis, this is noted in the relevant section.

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist (Appendix G of the NICE guidelines manual 2012) and the health economics review protocol in Appendix D of the full version of the guideline.

When no relevant economic studies were found from the economic literature review, relevant UK NHS unit costs related to the compared interventions were presented to the Committee to inform the possible economic implications of the recommendations.

## Number of Source Documents

See Appendix E: Clinical Article Selection and Appendix F: Economic Article Selection in the full guideline appendices (see the "Availability of Companion Documents" field) for flow charts and detailed information regarding the total number of articles identified, selected, and excluded for each guideline topic.

## Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

## Rating Scheme for the Strength of the Evidence

Overall Quality of Outcome Evidence in Grading of Recommendations Assessment, Development and Evaluation (GRADE)

| Level | Description |
|---|---|
| **High** | Further research is very unlikely to change confidence in the estimate of effect. |
| **Moderate** | Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate. |
| **Low** | Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. |
| **Very low** | Any estimate of effect is very uncertain. |

## Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

## Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Clinical Guideline Centre (NCGC) on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance and related appendices.

Evidence of Effectiveness

- Relevant studies were critically appraised using the appropriate checklist as specified in the National Institute for Health and Care Excellence (NICE) guidelines manual (see the "Availability of Companion Documents" field).
- Key information was extracted on the study's methods, according to the factors specified in the protocols and results. These were presented in summary tables (in each review chapter) and evidence tables (see Appendix H).
- Summaries of evidence were generated by outcome (included in the relevant review chapters) and were presented in Committee meetings:
    - Randomised studies: data were meta-analysed where appropriate and reported in Grading of Recommendations Assessment, Development, and Evaluation (GRADE) profiles (for intervention reviews).
    - Observational studies: data were presented as a range of values in GRADE profiles.
    - Prognostic studies: data were presented as reported by the authors, as adjusted odds ratios, risk ratios or hazard ratios along with the 95% confidence intervals. A range of values, usually in terms of the relative effect.
    - Diagnostic studies were presented as measures of diagnostic test accuracy (sensitivity, specificity and area under the curve).
    - Qualitative studies: each study was summarised by theme and meta-synthesis was carried out where appropriate to identify an overarching framework of themes and subthemes.

A 20% sample of each of the above stages of the reviewing process was quality assured by a second reviewer to eliminate any potential of reviewer bias or error.

Methods of Combining Clinical Studies

*Data Synthesis for Intervention Reviews*

Where possible, meta-analyses were conducted to combine the results of studies for each review question using Cochrane Review Manager (RevMan5) software. Fixed-effects (Mantel-Haenszel) techniques were used to calculate risk ratios (relative risk) for the binary outcomes, such as rate of adverse events or rate of people with symptom improvements.

For continuous outcomes, measures of central tendency (mean) and variation (standard deviation) were required for meta-analysis. Data for continuous outcomes (such as number of episodes of vomiting) were analysed using an inverse variance method for pooling weighted mean differences and, where the studies had different scales, standardised mean differences were used. A generic inverse variance option in RevMan5 was used if any studies reported solely the summary statistics and 95% confidence interval (95% confidence interval) or standard error; this included any hazard ratios reported. However, in cases where standard deviations were not reported per intervention group, the standard error (SE) for the mean difference was calculated from other reported statistics (p values or 95% confidence intervals); meta-analysis was then undertaken for the mean difference and SE using the generic inverse variance method in RevMan5. When the only evidence was based on studies that summarised results by presenting medians (and interquartile ranges), or only p values were given, this information was assessed in terms of the study's sample size and was included in the GRADE tables without calculating the relative or absolute effects. Consequently, aspects of quality assessment such as imprecision of effect could not be assessed for evidence of this type.

Where reported, time-to-event data were presented as a hazard ratio.

Stratified analyses were predefined for some review questions at the protocol stage when the Committee identified that these strata are different in terms of biological and clinical characteristics and the interventions were expected to have a different effect. For example, in the combined review on pharmacological symptom management for pain, anxiety, breathlessness, and agitation and delirium, people with reported individual symptoms were classified as strata because the Committee wanted to ideally make recommendations about the effectiveness of pharmacological treatments for specific symptoms.

Statistical heterogeneity was assessed by visually examining the forest plots, and by considering the chi-squared test for significance at p less than 0.1 or an I-squared inconsistency statistic (with an I-squared value of more than 50% indicating considerable heterogeneity). Where considerable

heterogeneity was present, the Guideline Committee carried out predefined subgroup analyses. For instance, in the pharmacological management of nausea and vomiting, causes leading to the symptom would be a subgroup. The guideline group also considered route of administration, delivery system, and drug class were also possible reasons for heterogeneity in results. Sensitivity analysis based on the quality of studies was also carried out, eliminating studies at overall high risk of bias (randomisation, allocation concealment and blinding, missing outcome data).

Assessments of potential differences in effect between subgroups were based on the chi-squared tests for heterogeneity statistics between subgroups. If no sensitivity analysis was found to completely resolve statistical heterogeneity then a random-effects (DerSimonian and Laird) model was employed to provide a more conservative estimate of the effect.

The means and standard deviations of continuous outcomes were required for meta-analysis. However, in cases where standard deviations were not reported, the standard error was calculated if the p values or 95% confidence intervals were reported and meta-analysis was undertaken with the mean and standard error using the generic inverse variance method in RevMan5.

For interpretation of the binary outcome results, differences in the absolute event rate were calculated using the GRADEpro software, for the median event rate across the control arms of the individual studies in the meta-analysis. Absolute risk differences were presented in the GRADE profiles and in clinical summary of findings tables, for discussion with the Committee.

For binary outcomes, absolute event rates were also calculated using the GRADEpro software using event rate in the control arm of the pooled results.

*Data Synthesis for Prognostic Factor Reviews*

Signs and symptoms that indicate someone is in the last days of life could be construed as a characteristic that predicts death occurring in the last days of life. This would be classified as a prognostic factor. In this respect odds ratios, risk ratios or hazard ratios, with their 95% for the effect of the pre-specified prognostic factors were extracted from the papers when reported. Evidence would come from observational studies because signs and symptoms that may indicate that someone is in the last days of life are not factors that could ever be randomised. For this topic the Guideline Committee looked for studies that took into account possible key confounders as reported in multivariable analyses. The reported measures would therefore be adjusted to take into account other characteristics less likely to be actual signs and symptoms of being in the last days of life. The studies did not adjust for this in a pre-specified manner, but used statistical methods that included variables that were likely signs and symptoms related to dying and modelled them using statistical methods (such as multivariable logistic regressions) which would then indicate which characteristics were the most likely independent prognostic factors rather than a factor only spuriously related. Data were not combined in meta-analyses for prognostic studies.

*Data Synthesis for Diagnostic Test Accuracy Reviews*

Data and Outcomes

Recognising dying could also be viewed akin to a diagnostic process in which you either display a sign or not and later identify people with or without the sign who have died in the next days. For this part it was anticipated that studies would report results indicating that the person had a particular sign as assessed by a value above a threshold value or could have a test along a continuously measured characteristic (such as kidney function tests for renal signs or symptoms). There are a number of diagnostic test accuracy measures. Area under the receiver operating characteristics (AUC of a ROC) curve shows true positive rate (sensitivity) as a function of false positive rate (1 minus specificity). Sensitivity, specificity, positive and negative predictive value, and positive and negative likelihood ratio would be reported. The threshold of a diagnostic test is defined as the value at which the test can best differentiate between those with and without the target condition (for instance a particular serum creatinine value) and, in practice, it varies amongst studies. For this particular question specificity was regarded as particularly important. When specificity is high, a positive test rules in the diagnosis and when sensitivity is high, a negative test rules out the diagnosis – researchers have created the mnemonic SoPin and SnNout for this. In other words in the case of high specificity with low sensitivity someone who has this sign or symptom (that is, akin to testing positive) would be likely to die within the next few days whereas for those who do not have the sign or symptom (akin to having a negative test) the Guideline Committee is uncertain about when they may die. Sensitivity (ruling out), was also recognised as being important in order not to miss people who may be dying in the next few days.

*Data Synthesis*

Diagnostic paired sensitivity-specificity forest plots would usually be produced for each sign or symptom, using RevMan5. In order to do this, 2×2 tables (the number of true positives, false positives, true negatives and false negatives) would be extracted.

However, the data that were identified in the 'recognising dying' chapter did not allow for direct extraction of 2×2 tables, because only summary data were presented (sensitivity and specificity with 95% confidence intervals).

Area under the ROC curve (AUC) data for continuous test results were given as AUC values with 95% confidence intervals. The accuracy of the test depends on how well the test separates the group being tested into those with and without the condition in question. The Committee agreed on the following criteria for AUC:

- ≤0.50: no better than chance
- 0.50–0.60: very poor
- 0.61–0.70: poor
- 0.71–0.80: moderate
- 0.81–0.92: good
- 0.91–1.00: excellent or perfect test

Diagnostic meta-analysis could not be carried out because 2x2 data could not be extracted.

*Data Synthesis for Qualitative Reviews*

Where possible a meta-synthesis was conducted to combine qualitative study results. The main aim of the synthesis of qualitative data was a description of the topics that may influence the experience of the person who is dying, those people important to them and healthcare professionals involved in their care, rather than build new theories or reconceptualise the topic under review. Whenever studies identified a qualitative theme, this was extracted and the main characteristics were summarised. When all themes were extracted from studies, common concepts were categorised and tabulated. This included information on how many studies had contributed to an identified overarching theme. In qualitative synthesis the frequency of themes across studies is not necessarily an indicator of the importance of a theme. The aim of qualitative research is to identify new perspectives on a particular topic. Hence study type and population in qualitative research can differ widely meaning that themes that may only be identified by 1 or a few studies can provide important new information. Therefore, for the purpose of the qualitative reviews in this guideline, the addition of studies was not exhaustive because the emphasis was on conceptual robustness rather than the quantitative completeness of evidence. This has implications for the types and numbers of studies that are included in qualitative reviews. Sampling continued until no new relevant data seemed to emerge regarding a topic either to extend or contradict it, a concept referred to as 'theoretical saturation' in the literature. The most relevant evidence in this respect would originate from studies set in a target context, that is, carried out in the UK National Health Service (NHS) setting. Therefore, when the evidence base was particularly large, the Guideline Committee was able to focus on UK studies only, but widened study inclusion when important perspectives were not or insufficiently covered. For instance, this was the case for barriers and facilitators in shared decision making where the Committee identified sufficient UK evidence on healthcare professionals' views, but only 1 UK study on family experiences of perspectives on shared decision making. The Committee therefore widened the inclusion to evidence from other countries to achieve theoretical saturation. The final selection of included or excluded studies from those that were identified in the literature search was carried out by at least 2 researchers. Themes from individual studies were then integrated into a wider context and when possible overarching categories of themes with sub-themes were identified. This was then placed into a thematic map that would present the relationship between themes and subthemes. The mapping part of the review was drafted by 1 researcher but the final framework of themes was further shaped and when necessary re-classified through discussions with at least 1 other researcher.

The Committee could then draw conclusions on the relative merits of each of the themes in each of the settings or countries and how they may help in forming recommendations.

*Integrative (Mixed Methods) Synthesis of Findings*

An integrative type of review allows for the inclusion of different study designs (both quantitative as well as qualitative) in order to fully understand an area of concern, that is, the signs and symptoms that may indicate that someone is in the last days of life. The quantitative section of the review included both prognostic and diagnostic components (described in the relevant sections above). The incorporation of qualitative elements (perspective on recognising dying from healthcare professionals and information from published Delphi consensus surveys) would provide additional information to purely quantitative data which may be limited in quantity in this area (see data synthesis for qualitative reviews above). An 'integrative review' has all of the components of other systematic reviews that are regularly used in NICE guideline development, but further to the synthesis of the relevant studies it includes a thematic analysis to provide a conceptual map of the topic (that is, a theoretical framework). The results are presented as a summary and narrative synthesis and would therefore capture results that may not be directly apparent from a quantitative or narrative synthesis alone (such as the uncertainties of recognising the signs in the final days of life which will have implications for all other topics in this guideline).

Appraising the Quality of Evidence Using 'Grading of Recommendations Assessment, Development and Evaluation' (GRADE)

For intervention reviews, the evidence for outcomes from the included RCTs and observational studies were evaluated and presented using GRADE developed by the international GRADE working group (http://www.gradeworkinggroup.org/ ). Modified

GRADE assessments were also carried out for outcomes per risk factor in prognostic reviews, for accuracy measures in diagnostic reviews and themes in qualitative reviews.

The software developed by the GRADE working group (GRADEpro) was used to assess the quality of each outcome, taking into account individual study quality factors and the meta-analysis results. This software is used mainly for intervention reviews, but can also be used for prognostic reviews. It is not presently designed to assess evidence from diagnostic and qualitative reviews. Therefore the modified GRADE approach for diagnostic and qualitative evidence was carried out without the software but using similar tables and concepts which are described below. Results were presented in GRADE profiles ('GRADE tables'), which consist of 2 sections: the 'Clinical evidence profile' table includes details of the quality assessment while the 'Clinical evidence summary of findings' table includes pooled outcome data, where appropriate, an absolute measure of intervention effect and the summary of quality of evidence for that outcome. In this table, the columns for intervention and control indicate summary measures and measures of dispersion (such as mean and standard deviation or median and range) for continuous outcomes and frequency of events (n/N: the sum across studies of the number of people with events divided by sum of the number of completers as well as 95% confidence intervals) for binary outcomes. Reporting or publication bias was only taken into consideration in the quality assessment and included in the 'Clinical evidence profile' table if it was apparent.

See Chapter 4 in the full version of the guideline for additional details on the quality elements examined.

The GRADE toolbox is currently designed only for randomised trials and observational studies but the Guideline Development Group (GDG) adapted the quality assessment elements and outcome presentation for all other review types, that is; diagnostic, prognostic and qualitative studies.

Grading the Quality of Clinical Evidence

After data were synthesised, the overall quality of evidence was assessed for each outcome (in intervention or prognostic reviews), by diagnostic sign and symptom, or qualitative theme. The following procedure was adopted when using GRADE:

1. A quality rating was assigned, based on the study design. RCTs start as High in intervention review, observational studies as Low, and uncontrolled case series as Low or Very low. In diagnostic, prognostic and qualitative reviews, evidence from non-randomised studies start as High.
2. The rating was then downgraded for the specified criteria: risk of bias (study limitations), inconsistency, indirectness, imprecision and publication bias. These criteria are detailed in the full version of the guideline. In intervention reviews, evidence from observational studies (which had not previously been downgraded) was upgraded if there was: a large magnitude of effect, a dose–response gradient, and if all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results showed no effect. Each quality element considered to have 'serious' or 'very serious' risk of bias was rated down by 1 or 2 points respectively.
3. The downgraded or upgraded marks were then summed and the overall quality rating was revised. For example, all RCTs started as High and the overall quality became Moderate, Low or Very low if 1, 2 or 3 points were deducted respectively.
4. The reasons or criteria used for downgrading were specified in the footnotes.

The details of the criteria used for each of the main quality element are discussed further in Sections 4.2.10 to 4.2.13 of the full version of the guideline.

Evidence Statements

Evidence statements are summary statements that are presented after the GRADE profiles, summarising the key features of the clinical effectiveness evidence presented.

The narrative evidence statements focus on the critical outcomes and encompass key features of the evidence, such as:

- The number of studies and the number of participants for a particular outcome
- A brief description of the participants
- An indication of the direction of effect a description of the overall quality of evidence (GRADE overall quality)

Qualitative evidence statements provide a summary of the themes identified along with characteristics listed above. A statement is also given where no evidence is identified.

Evidence of Cost-effectiveness

The Committee is required to make decisions based on the best available evidence of both clinical and cost effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits (that is, their 'cost-effectiveness') rather than the total implementation cost. Thus, if the evidence suggests that a strategy provides significant health benefits at an

acceptable cost per person treated, it should be recommended even if it would be expensive to implement across the whole population.

Evidence on cost effectiveness related to the key clinical issues being addressed in the guideline was sought. The health economist undertook a systematic review of the published economic literature.

The health economist:

- Critically appraised relevant studies using the economic evaluations checklist as specified in the NICE guidelines manual.

Studies initially considered eligible but which were then excluded can be found in Appendix M with reasons for exclusion explained.

## Methods Used to Formulate the Recommendations

Expert Consensus

Informal Consensus

## Description of Methods Used to Formulate the Recommendations

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Clinical Guideline Centre (NCGC) on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance and related appendices.

Who Developed This Guideline?

A multiprofessional Guideline Committee comprising health professionals and researchers as well as lay members developed this guideline.

The National Institute for Health and Care Excellence (NICE) funds the National Clinical Guideline Centre (NCGC) and thus supported the development of this guideline. The Committee was convened by the NCGC and chaired in accordance with guidance from NICE.

The Committee met every 5 to 6 weeks during the development of the guideline. Staff from the NCGC provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers, health economists and information scientists. They undertook systematic searches of the literature, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate and drafted the guideline in collaboration with the Committee.

Developing Recommendations

Over the course of the guideline development process, the Committee was presented with:

- Evidence tables of the clinical and economic evidence reviewed from the literature. All evidence tables are in the Appendices (H and I).
- Summaries of clinical and economic evidence and quality (as presented in Chapters 5-10 in the full version of the guideline).
- Forest plots and summary Receiver Operating Characteristics (ROC) curves (Appendix K).
- A description of the methods and results of the cost-effectiveness analyses undertaken for the guideline (Appendix N).

Recommendations were drafted on the basis of the Committee's interpretation of the available evidence, taking into account the balance of benefits, harms and costs between different courses of action. This was either done formally in an economic model, or informally. Firstly, the net benefit over harm (clinical effectiveness) was considered, focusing on the critical outcomes. When this was done informally, the Committee took into account the clinical benefits and harms when 1 intervention was compared with another. The assessment of net benefit was moderated by the importance placed on the outcomes (the Committee's values and preferences), and the confidence the Committee had in the evidence (evidence quality). Secondly, whether the net benefit justified any differences in costs was assessed.

When clinical and economic evidence was of poor quality, conflicting or absent, the Committee drafted recommendations based on their expert opinion. The considerations for making consensus-based recommendations include the balance between potential harms and benefits, the economic costs compared with the economic benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The consensus recommendations were agreed through discussions in the Committee. The Committee also considered whether the uncertainty was sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation.

The Committee considered the 'strength' of recommendations. This takes into account the quality of the evidence but is conceptually different.

Some recommendations are 'strong' in that the Committee believes that the vast majority of healthcare and other professionals and patients would choose a particular intervention if they considered the evidence in the same way that the Committee has. This is generally the case if the benefits clearly outweigh the harms for most people and the intervention is likely to be cost effective. However, there is often a closer balance between benefits and harms, and some people would not choose an intervention whereas others would. This may happen, for example, if some people are particularly averse to some side effect and others are not. In these circumstances the recommendation is generally weaker, although it may be possible to make stronger recommendations about specific groups of people.

The Committee focused on the following factors in agreeing the wording of the recommendations:

- The actions health professionals need to take
- The information readers need to know
- The strength of the recommendation (for example the word 'offer' was used for strong recommendations and 'consider' for weak recommendations)
- The involvement of patients (and their carers if needed) in decisions on treatment and care
- Consistency with NICE's standard advice on recommendations about drugs, waiting times and ineffective interventions

For recommendations where there was equivocal, limited or no evidence, for example for signs or symptoms or drugs, alphabetical ordering of lists were used to rather than prioritize based solely on the Committee consensus.

The main considerations specific to each recommendation are outlined in the 'Recommendations and link to evidence' sections within each chapter of the full version of the guideline.

## Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Some recommendations can be made with more certainty than others. The Guideline Committee makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the Guideline Committee is confident that, given the information it has looked at, most patients would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

Interventions That Must (or Must Not) Be Used

The Guideline Committee usually uses 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally the Guideline Committee uses 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Interventions That Should (or Should Not) Be Used – a 'Strong' Recommendation

The Guideline Committee uses 'offer' (and similar words such as 'refer' or 'advise') when confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. The Guideline Committee uses similar forms of words (for example, 'Do not offer…') when confident that an intervention will not be of benefit for most patients.

Interventions That Could Be Used

The Guideline Committee uses 'consider' when confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

## Cost Analysis

Undertaking New Health Economic Analysis

As well as reviewing the published economic literature for each review question the feasibility of developing a new economic analysis was discussed with the Committee. A new economic analysis was not undertaken for this guideline given the lack of good quality clinical data and the issues related to settings and uncertainties around the quantification of health benefit in the last few days of life.

Cost-effectiveness Criteria

The National Institute for Health and Care Excellence (NICE) report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that the Committee should consider when judging whether an intervention offers good value for money.

In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- The intervention provided clinically significant benefits at an acceptable additional cost when compared with the next best strategy

In the Absence of Economic Evidence

When no relevant published studies were found, the Committee made a qualitative judgement about cost-effectiveness by considering expected differences in resource use between options and relevant UK National Health Service (NHS) unit costs, alongside the results of the clinical review of effectiveness evidence.

The UK NHS costs reported in the guideline are those that were presented to the Committee and were correct at the time recommendations were drafted. They may have changed subsequently before the time of publication but the Committee has no reason to believe they have changed substantially.

## Method of Guideline Validation

External Peer Review

Internal Peer Review

## Description of Method of Guideline Validation

Validation Process

This guidance is subject to a 6-week public consultation and feedback as part of the quality assurance and peer review of the document. All comments received from registered stakeholders are responded to in turn and posted on the National Institute for Health and Care Excellence (NICE) Web site.

# Evidence Supporting the Recommendations

## Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

Type of Studies

For most intervention reviews in this guideline, parallel randomised controlled trials (RCTs) were included because they are considered the most robust type of study design that could produce an unbiased estimate of the intervention effects. The Committee believed that there would be limited evidence of this type (due to the study population being in the last days of life); therefore non-randomised studies were also considered.

For diagnostic reviews, cross-sectional and retrospective studies were included. For prognostic reviews, prospective and retrospective cohort studies were included. Case–control studies were not included.

Where data from observational studies were included, the Committee decided that the results for each outcome should be presented separately for each study and meta-analysis was not conducted.

# Benefits/Harms of Implementing the Guideline Recommendations

## Potential Benefits

- The clinical signs and symptoms identified in the review are non-invasive tests or measures and therefore should not cause any harm to the dying person. Benefits of correctly recognising imminent death may allow opportunity for shared decision-making and allow valuable time between the dying person and those important to them.
- Adequate communication of prognosis improves the end of life care of dying people. It also improves the post death bereavement experiences of people important to the dying person, although this was not evidenced in the literature reviewed.
- For people already dying in hospital, anticipatory prescribing may allow the multidisciplinary team to prescribe appropriately in-hours, and also reduce delays in getting both the drugs and a prescriber to the dying person when symptoms arise.

Refer to the "Trade-off between clinical benefits and harms" sections in the full version of the guideline (see the "Availability of Companion Documents" field) for additional discussion of benefits of specific interventions.

## Potential Harms

- The dying person and those important to them should be made aware of any potential harms of clinically assisted hydration, such as the need for intravenous cannulation or insertion of a subcutaneous needle, pooling of fluids in subcutaneous tissues, fluid overload causing increased respiratory secretions and the possibility of moving care setting if clinically assisted hydration cannot be provided in the community.
- The Committee discussed the potential harm of over-treating people in the last days of life in terms of the risk for adverse effects and hastening death, or the perception of hastening death. The Committee discussed the potential harm of over- or under-treating people in the last days of life in terms of the risk of adverse effects, or the perception of hastening death. The Committee considered potential harms to include unwanted sedation, which can lead to the dying person not being conscious to engage with loved ones in last days of life. Potential harms should be minimised by considering the choice of pain management in light of medication already being administered.
- The Committee commented on the potential harms of using opioids to manage breathlessness if not prescribed appropriately. Harms discussed included over suppression of respiratory drive which could hasten death. They also commented on the use of oxygen therapy in those with chronic obstructive pulmonary disease (COPD) in the last days of life which, if not treated properly, can lead to loss of respiratory drive in these people.
- The Committee noted that there are potential adverse side effects such as unwanted sedation with antipsychotic agents. However, consideration was also needed as to how prescribed medications interact with other concomitant medications being used to manage other symptoms in the last days of life. Combining certain medications could have a cumulative sedative effect potentially causing harm. No evidence was identified for adverse effects of treatment linked to extrapyramidal side effects, but the Committee discussed dystonia and that this may occur, particularly in those that are neuroleptically naïve.
- One concern raised in the More Care Less Pathway review was injudicious administration and prescription of medication by inexperienced staff, possibly unfamiliar with the person, who may use inappropriate doses or drugs or even incorrectly assess that the person is dying. This may cause harm either by undertreating symptoms or by causing detrimental side effects including hastening a person's death when potentially reversible conditions are missed. Once medications are started it can be difficult to stop them and may require advice from a health care professional experienced in end of life care. Another concern is the potential waste of drugs as any unused medications already dispensed in the community have to be discarded. It is also important to consider the psychological impact of a 'just in case box' for the dying person and those important to them, which could be perceived either as anxiety provoking or reassuring depending on the explanation that is proffered by the responsible health care professional. There are undoubtedly risks that need to be weighed up with the storage of controlled drugs and other drugs of abuse including the possibility of diversion and access and use by unauthorised individuals.
- The Committee voiced concerns about the management and monitoring of over-use of drugs, highlighting the possibility of over-medicating the dying. In contrast, other concerns around the under-use of drugs were also considered.

Refer to the "Trade-off between clinical benefits and harms" sections in the full version of the guideline (see the "Availability of Companion Documents" field) for additional discussion of harms of specific interventions.

# Contraindications

## Contraindications

### Contraindications

The Committee noted that there were contraindications in using some antiemetics, for example, the use of cyclizine in people with severe heart failure or prokinetics in people with mechanical bowel obstruction.

# Qualifying Statements

## Qualifying Statements

- Healthcare professionals are expected to take National Institute for Health and Care Excellence (NICE) clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and, where appropriate, their guardian or carer.
- Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by practitioners in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.
- The National Clinical Guideline Centre (NCGC) disclaims any responsibility for damages arising out of the use or non-use of this guideline and the literature used in support of this guideline.

# Implementation of the Guideline

## Description of Implementation Strategy

Implementation: Getting Started

This section highlights three areas of the care of dying adults in the last days of life guideline that could have a big impact on practice and be challenging to implement, along with the reasons why change is happening in these areas (given as a note at the start of each area). The Guideline Development Group (GDG) identified these with the help of stakeholders and Guideline Committee members. The section also gives information on resources to help with implementation. Refer to the original guideline document for specific information on these areas.

Further resources are available from the National Institute for Health and Care Excellence (NICE) that may help to support implementation.

- Annual indicators for use in the Quality and Outcomes Framework (QOF) for the UK. See the process and the NICE menu .
- Uptake data about guideline recommendations and quality standard measures
- The Royal College of Physicians' National care of the dying audit of hospitals can help providers to audit their care against national standards and policies

## Implementation Tools

Audit Criteria/Indicators

Mobile Device Resources

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

# Institute of Medicine (IOM) National Healthcare Quality Report Categories

## IOM Care Need

End of Life Care

## IOM Domain

Effectiveness

Patient-centeredness

# Identifying Information and Availability

## Bibliographic Source(s)

National Clinical Guideline Centre. Care of dying adults in the last days of life. London (UK): National Institute for Health and Care Excellence (NICE); 2015 Dec 16. 26 p. (NICE guideline; no. 31).

## Adaptation

Not applicable: The guideline was not adapted from another source.

## Date Released

2015 Dec 16

## Guideline Developer(s)

National Guideline Centre - National Government Agency [Non-U.S.]

## Source(s) of Funding

The National Clinical Guideline Centre (NCGC) was commissioned by the National Institute for Health and Care Excellence (NICE) to undertake the work on this guideline.

## Guideline Committee

Guideline Committee

## Composition of Group That Authored the Guideline

*Guideline Committee Members*: Sam Ahmedzai (*Chair*), Professor of Palliative Medicine Department of Oncology, School of Medicine and Biomedical Science, The University of Sheffield; Adam Firth, General Practitioner, Bracondale Medical Centre; Adrian Blundell, Consultant Geriatrician, Honorary Associate Professor in Medicine of Older People, Nottingham University Hospital; Annette Furley, Lay Member; Cheryl

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## Financial Disclosures/Conflicts of Interest

At the start of the guideline development process all Committee members declared interests including consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry, in accordance with the National Institute for Health and Care Excellence (NICE) guidelines manual 2012 (see the "Availability of Companion Documents" field). At all subsequent Committee meetings, members declared arising conflicts of interest.

Guideline Committee members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in Appendix B (see the "Availability of Companion Documents" field).

## Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

## Guideline Availability

Available from the National Institute for Health and Care Excellence (NICE) Web site . Also available for download in ePub or eBook formats from the NICE Web site .

## Availability of Companion Documents

The following are available:

- Care of dying adults in the last days of life. Full guideline. London (UK): National Institute for Health and Care Excellence; 2015 Dec. 270 p. (NICE guideline; no. 31). Available from the National Institute for Health and Care Excellence (NICE) Web site .
- Care of dying adults in the last days of life. Appendices. London (UK): National Institute for Health and Care Excellence; 2015 Dec. 362 p. (NICE guideline; no. 31). Available from the NICE Web site .
- Care of dying adults in the last days of life. Baseline assessment tool. London (UK): National Institute for Health and Care Excellence; 2015 Dec. (NICE guideline; no. 31). Available from the NICE Web site .
- Care of dying adults in the last days of life. Costing report. London (UK): National Institute for Health and Care Excellence; 2015 Dec. 4 p. (NICE guideline; no. 31). Available from the NICE Web site .
- The guidelines manual 2012. London (UK): National Institute for Health and Care Excellence (NICE); 2012 Nov. Available from the NICE Web site .

Quality indicators are available from the NICE Web site and the Royal College of Physicians Web site .

## Patient Resources

The following is available:

- Caring for adults in their last days of life. Information for the public. London (UK): National Institute for Health and Care Excellence; 2015 Dec. 10 p. (NICE guideline; no. 31). Available from the National Institute for Health and Care Excellence (NICE) Web site

. Also available for download in eBook and ePub formats from the NICE Web site .

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## NGC Status

This NGC summary was completed by ECRI Institute on March 17, 2016. This summary was updated by ECRI Institute on May 24, 2016 following the U.S. Food and Drug Administration advisory on Olanzapine. This summary was updated by ECRI Institute on June 2, 2016 following the U.S. Food and Drug Administration advisory on opioid pain medicines. This summary was updated by ECRI Institute on October 21, 2016 following the U.S. Food and Drug Administration advisory on opioid pain and cough medicines combined with benzodiazepines.

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